

Procter & Gamble

The Procter & Gamble Company
Winton Hill Technical Center
6071 Center Hill Avenue, Cincinnati, Ohio 45224-1703

2683 '00 MAR -6 A9:29

March 3, 2000

Docket Management Office
5630 Fisher's Lane
Rockville, MD 20852

Dear Madam:

We wish to submit the enclosed report and cover letter entitled "Post Marketing Surveillance Committee Summaries" to the olestra docket #00F-0792 so that they are publicly available. This Committee is composed of Drs. J. Freston, D. Ahnen, S. Czinn, D. Jones, and R. Sandler. The Committee has met seven (7) times to review alleged adverse event reports associated with consumption of olestra snacks. The Committee has concluded following each review that based on review of the reports, there is no reason to believe that olestra represents a cause for public health concern. These summaries have been previously submitted to Mary Ditto of FDA's Office of Pre-market Approval.

Please let me know if you have any questions (513-634-6808).

Thank you.

Sincerely,

THE PROCTER & GAMBLE COMPANY



Greg Allgood, Ph.D.
Associate Director
Regulatory & Clinical Development

Enclosure

00F-0792

RPT1

Olestra Post Marketing Surveillance Committee

1st Meeting

MINUTES OF COMMITTEE MEETING

TO REVIEW THE ADVERSE EVENT REPORTS ARISING FROM THE INITIAL SIX MONTHS OF THE OLESTRA SURVEILLANCE PROGRAM

Present: Dr J Freston, University of Connecticut, Farmington, CT
Dr D Ahnen, VA Hospital, Denver, CO
Dr S Czinn, Rainbow Babies and Children's Hospital: Pediatric GI
and Nutrition, Cleveland, OH
Dr D Jones, Degge Group Ltd, Arlington, AV
Dr R Sandler, University of North Carolina, Chapel Hill, NC

1. Introduction and purpose of the meeting

- This meeting was convened to review the alleged adverse event reports received by Procter and Gamble during the first six months of the olestra passive safety surveillance program. During this period, olestra products were available in Cedar Rapids, IA, Grand Junction, CO and Eau Claire, WI). Near the end of this period (September 1996) products became available in Columbus, OH.
- The meeting was independently arranged with the Committee members appointed and briefed by Strategic Consultants International (SCI), UK. The adverse event reports arising from the surveillance program were dispatched by Procter and Gamble to SCI who subsequently developed the committee meeting agenda, assigned responsibilities among the Committee members and then forwarded the reports to the participants for review before the meeting.
- The main purpose of the Committee meeting was to review the type, incidence and severity of the alleged adverse event reports by those consuming olestra and to assess if they posed any clinically significant cause for concern.
- The Committee were also asked to provide suggestions and recommendations for how the safety reports could be optimally presented and evaluated.

2. Prioritizing incoming calls

- Both Frito Lay and Procter and Gamble operate a 'zero tolerance' phone in system for adverse event reports in which callers are not put on hold for extended lengths of time. To date there have been 360 calls and there was a decrease in the number of adverse events in the second three month period.

- To date the test markets have been relatively small and the system has been able to handle calls on this 'zero tolerance' basis. This will need to be revised with the addition of Columbus. Moreover, the national launch could overwhelm the system if all calls are treated similarly.
- Therefore, while the Committee appreciated that the current reporting system is helpful in identifying adverse event 'signals', they suggested that serious medical issues could be prioritized and enter into a different, intensive, follow up system. Moreover, they suggested that calls from consumers eating very few chips should be reported separately so they did not detract from reports from those eating a more substantial serving of olestra.
- To date there have been 37 reports of people alleging that they have had to seek health care advise as a result of the adverse event they experienced after eating olestra (17 outpatients, 6 Emergency Room attendances, 2 Hospitalizations and 2 reports for which the details are unknown, despite repeated follow up attempts). In all these cases medical records have been requested but to date records are only available on five cases.
- The Committee emphasized the importance of following up these cases very energetically to obtain the relevant medical records. They pointed out that these could provide valuable insight into the overall circumstances of the person reporting the adverse event, which may help set it into appropriate perspective.
- All those reporting an adverse event are offered the opportunity to participate in a rechallenge test.

3. The Committee's comments on the adverse event reports

- There were no concerns about the demographics of the adverse event reports. In particular, there were no concerns about the reports from children consuming olestra. An over representation of females was noted, probably because they are often responsible for family health care.
- In reviewing the reports by test markets it was noted that reports were being received from states outside the test market areas. This could be accounted for by consignments of chips being shipped to non test site cities.
- It was recommended that a special effort was made to follow up people reporting very frequent bowel motions as this would provide valuable background data which may help objective assessment of any association of the olestra consumption with the increase in bowel motions. The Committee did not feel that there was much value in reporting the consistency of the BMs and suggested that this was dropped.
- The Committee considered that the key features for evaluating the individual Case Narratives included the seriousness of the report, likely causality with respect to olestra and the occurrence of unusual reports. Using this as a base, the Committee evaluated the reports from consumers alleging that they required medical assistance. In review of this data, the Committee did not note any cases of particular medical concern.

- The rechallenge data was reviewed and the only noticeable difference in reporting between the triglyceride and olestra - containing chips was in 'other GI symptoms' - specially flatulence and bloating.
- The Committees felt that the rechallenge data was of particular importance and that the results should be reported along side the original entry or cross referenced.
- Finally the Committee recommended a database be constructed of all the adverse event reports which would facilitate their review and overall evaluation. This would include the following categories:

Age
 Gender
 Geography/locale
 Type of product consumed (chips, tortillas or Nachos)
 Amount olestra consumed
 Symptoms reported (COSTART, severity, frequency etc.)
 Time to onset of symptoms
 Duration of symptoms
 Concomitant disease/treatments
 Number of Bowel Motions
 Requirement of a visit to medical facility
 Other members of the family affected
 Outcome
 Results of rechallenge data if known

4. Conclusions

- Having reviewed the results of the first two, three month periods (or first six months), in depth, the Committee found that the reports did not present a public health concern

5. Next meeting

- The next meeting of the Committee was agreed for Thursday 5th June 1997, Chicago, IL

Olestra Post Marketing Surveillance Committee

2nd Meeting
June 5th, 1997



STRATEGIC · CONSULTANTS · INTERNATIONAL · plc

August 15th 1997

AH/JOD/PMSC/FDAMSL.DOC

Mary Ditto PhD
Food & Drug Administration
1110 Vermont Avenue, NW
HFS-207, 12th Floor
Washington, DC 20005
USA

Dear Dr. Ditto,

Re: Minutes of olestra Post Marketing Surveillance Committee

Please find enclosed copies of the Minutes based on the findings of a recent meeting of the Olestra Post Marketing Surveillance Committee which was convened on June 5th 1997 to review the adverse events reported in the program by people consuming olestra-containing foods. The objective was to determine if these reports indicated any cause for medical concern. The panel is comprised of experts in the fields of gastroenterology, pharmacovigilance and epidemiology. The meeting was convened independently by Strategic Consultants International UK, and was funded by Procter & Gamble.

For convenience, Procter and Gamble asked SCI to submit these Minutes to you directly and we understand that they have already discussed this with you.

Questions about the Minutes per se and the experts' roles should be directed to SCI, but any points concerning the data should be directed to Procter and Gamble.

Yours sincerely,

ALISON L. HOWE
Managing Director
Strategic Consultants International
Direct Line 44-(0)1442-210161 (UK)

Encs: Minutes

Summary of the Second Meeting of the Olestra Post Marketing Surveillance Advisory Committee

June 5th 1997, Fairmont Hotel, Chicago

Attendees:

Dr R Sandler, Chairman, University of North Carolina, Chapel Hill, NC

Dr D Ahnen, VA Hospital, Denver, CO

Dr S Czinn, Rainbow Babies & Children's Hospital, Cleveland, OH

Dr J Freston, University of Connecticut, Farmington, CT

Dr J Jones, Degge Group Ltd, Arlington, AV

1. Welcome and objectives of the Committee

- Dr Sandler welcomed the Committee and outlined a mission statement he had developed for the Committee's considerations:

The mission of the Olestra Post Marketing Surveillance Advisory Committee is to provide independent review of adverse experiences associated with olestra consumption and to make recommendations about the safety of olestra.

Dr Sandler requested that the Committee consider this statement and provide comments to him after the meeting.

- Dr Sandler also stated the objectives for the Committee:

In order to make recommendations about the safety of olestra the Advisory Committee will review and evaluate:

- individual reports of adverse experiences that are collected and assembled by Procter & Gamble
- detailed narrative reports of individuals who sought medical attention due to adverse experiences
- individual and aggregate data from rechallenge testing

The Committee will use this information to make recommendations to Procter & Gamble about whether olestra consumption represents a health risk.

2. Update on test market statistics

- The test markets in Eau Claire, WI; Grand Junction, CO and Cedar Rapids, IA are complete. There are test markets currently ongoing in Columbus for Pringles, Indianapolis for Frit-o-Lay and in Marion for Nabisco

- The adverse event rates are:

	B Scan	Ohio	Indiana
Total # reports	117	352	555
Calls/per 100,000 pop	23	18	16
Physician contacts	9(7.7%)	23(6.5%)	37(6.7%)

- The call rates are higher as the test market opens and then reduce to a low steady level.

3. **Review of a population -based survey of digestive complaints in Indianapolis. Implications for the olestra surveillance program**

- The highlights of this study are as follows.

Methods: The survey was conducted between February 17-25th 1997, 1 week prior to the Indianapolis test market opening. One person in 454 randomly selected households was interviewed in a structured questionnaire which asked about their demographics and GI symptom frequency.

Outline results: Episodic digestive complaints, including cramps, gas and diarrhea are common - more than 25% of the respondents reported one or more.

Symptoms were perceived as moderate to severe in intensity, 30-40% took medications and 11-14% consulted physicians.

A number of foods such as beans commonly produce digestive complaints but people eat them anyway

Implications: Because episodic digestive complaints are common, it is not surprising that symptoms are reported during the olestra post marketing surveillance.

- Dr Ahnen suggested that it might be helpful if the questions in Dr Sandler's next national survey reflect the type of questions asked in the test market surveillance program (eg Have you seen a physician for these symptoms in the past two years?)
- Dr Sandler queried how compatible the two populations would be as the reports from the test markets probably represent a skewed population which drives them to call/complain.

- Dr Czinn suggested that the next survey should include children.

4. Update on the latest studies with olestra

(A) Theater Test

Investigator: Lawrence Cheskin,
John Hopkins Medical School, Boston

Design: Randomized, double blind, parallel group (Olean vs control), single center study involving 1400 adults (n=700 in each group).

The study was calculated to have sufficient power to detect a 5% difference in GI symptoms.

Products: Frito Lay Max Ruffles (Olean) or Frit-o-Lay regular Ruffles in 13oz bags with choice of 32 oz beverage

Venue: Multiplex movie theater in Chicago

Endpoints: GI symptoms elicited by telephone recall, 2-3 days post movie, via open - ended questions. Chip consumption was weighed.

Results: 1092 evaluable subjects
84% of survey was completed in 2-4 days , 98% overall
All reported GI symptoms from recall were coded using a modified COSTART dictionary

25th percentile consumption	1.3 oz
50th percentile consumption	2.4 oz
75th percentile consumption	3.9 oz

- The adverse event s reported are as follows:

1 or more GI events	15-16% (similar in two groups with slightly less for Olean)
Gas	4-6%(similar in both groups, with slightly less for Olean)
Rest	1-2% (similar in both groups)

There were no oil leak reports

There was a similar level of severity of events for Olean and full fat chips

Two reports of diarrhea - both in people consuming full fat chips

(B) Home test

Design: 6 week, randomized, double blind, placebo controlled study involving 3000 households eating chips ad libitum

Diary cards are used to log a variety of GI symptoms. Those reporting and adverse experience are asked how this affected their daily activities: did they take medication for the condition or consult a physician?

<i>Products:</i>	Test group	Comparison group
	Olestra Olean labeled products	Triglyceride chips marketed as Olean
	Regular triglyceride chips In standard market packages	Regular triglyceride chips in standard market packages

- Dr Czinn thought that the questions might need modifying for children as they were too complex/ not appropriate.

c. Stool test

Investigator: Dr Gianella, Cincinnati

Design: Subjects eat 20-30grams of olestra with and without sorbitol and feces are collected for electrolytes and water

- results are awaited from the latter two studies

5. Methods of assessing adverse events in the context of post marketing surveillance and the application to olestra

- The objective for assessing adverse events is to devise a means of attaining an objective score.
- Dr Jones outlined several methods used to assess adverse events which estimate the probability that the event was caused by the product under surveillance.
- Dr Jones recommended an algorithm approach for the assessment of olestra adverse event reports. This assigns causality based on:

Timing
Event character

Product type
Dose
Symptoms
Past history of allergies/illnesses

- Dr Jones presented an assessment algorithm for the consideration of the Committee. This was reviewed in depth and then modified after application to several of the case reports of people who reported consulting a physician in the context of their alleged adverse event.
- The algorithm, as finally agreed by the Committee, is attached in Appendix 1

6(a) In adverse events with no physician contact, does the dose of olestra consumed affect the type and severity of the alleged adverse event?

- Dr Ahnen had coded the GI events (diarrhea, abdominal pain, flatulence, nausea and vomiting, bloating and abnormal stool) versus 'other' events (a wide spectrum of 38 different symptom terms).
- When the incidence of these adverse events were plotted against dose, it was observed that the incidence of diarrhea and abdominal pain *decreased* with doses in excess of 30-40 grams olestra. The incidence of 'other' and abnormal stool *increased* over 40-50 grams consumption of olestra.
- It was acknowledged that the 'other' category was very broad and combined a lot of different individual reports and therefore was difficult to interpret.

6(b) In adverse events with no physician contact, does the dose of olestra consumed affect the onset and duration of symptoms?

- Dr Freston reported the following observations as a result of reviewing all the data:

Dose grms	n	Time to onset of symptoms	
		Hours	
		1 hour or less	2-6 hours
0-5	135	16	32
5-10	141	22	42
10-20		11	42
20-30		17	37
30		4	57
40-50		8	50
>50		3	11

- The Committee agreed that if an adverse event is reported >4 days after the time of ingestion, this is unlikely to be causally related to the ingestion of olestra.
 - The Committee agreed that there was nothing of concern with respect to the duration of the symptoms and the dose of olestra.
- 6(c) **In adverse events with no physician contact, does the age of the consumer influence the alleged reports?**
- Dr Czinn reported that there was no indication that olestra would put children or the elderly at risk.

Overall conclusions to section 6

- The Committee did not derive any association between the dose of olestra consumed, the age of the consumer or the time to onset of symptoms reported after consuming olestra.
- Oily stool appeared to be more likely if ≥ 40 grams olestra consumed.
- Symptoms reported > 4 days after olestra consumption are unlikely to be related to olestra.
- There was no cause for concern found in the alleged adverse events associated with the consumption of olestra.

7. **Evaluation of reports from the Rechallenge Test**

- This was considered to be important data
- It was agreed that the aggregate rechallenge data should be reviewed - not individual reports.
- The Committee did not find any cause for concern with the data
- It was recommended that the results of the Rechallenge Test should be written up in the form of a clinical trial and submitted for publication

8. **CONCLUSIONS**

- **The Committee agreed that the type, severity and duration of symptoms reported in the olestra passive surveillance program does not pose any cause for concern**

9. **Next Committee meeting**

- The date of the next Committee meeting will be November 6th at the Fairmont Hotel, Chicago.
- For this meeting the Committee will need to review the following data:
 - Case reports of all 'serious' adverse events and those events which involved a physician visit
 - Death or life threatening
 - Requiring hospitalization
 - Visit to emergency room
 - Physician visit
 - Case reports of adverse events in which the following are reported:

- oily stool	- clothing stains
- rash	- edema
- bloody stool	- burning mouth
- The incidence of the rest of the reports should be plotted by dose and by age. It was requested that the adverse reports for the 0 -5gram consumption should be displayed.

Olestra Post Marketing Surveillance Committee

3rd Meeting
November 6th, 1997

Minutes of the Olestra Post Marketing Surveillance Advisory Committee

Chicago, November 6th 1998

Attendees:	R. Sandler	: Chairman, University of North Carolina, Chapel Hill, NC
	D. Ahnen	: VA Hospital, Denver, CO
	S. Czinn	: Rainbow Babies and Children's Hospital, Cleveland, OH
	J. Freston	: University of Connecticut, Farmington, CT
	J. Jones	: Degge Group Ltd, Arlington, AV
	J. McRorie	: <i>Presentation only, Procter & Gamble, Cincinnati, OH</i>
	N. Zorich	: <i>Presentation only, Procter & Gamble, Cincinnati, OH</i>
	M. Ditto	: <i>FDA, Washington DC</i>
	T. Wilcox	: <i>FDA, Washington DC</i>

1. Objectives of the meeting

- The Chairman, Dr Robert Sandler, restated the mission of the Olestra Post Marketing Surveillance Committee is to provide an independent review of the adverse experiences reported by olestra consumers and to make recommendations about the safety of olestra (attachment 1).
- In order to make these recommendations Dr Sandler asked the Committee to review :
 - the aggregated adverse events reported to Procter & Gamble for the period March 22nd - July 22nd 1998
 - the detailed narrative reports of those individuals who sought medical advice related to the adverse events
 - the data from those who entered the olestra double blind rechallenge study
- Before reviewing the adverse event reports there were several presentations which summarized for the Committee members the results of recent studies of relevance to the overall assessment of the safety and tolerability of olestra. These will be reported very briefly as the speakers provided self explanatory hard copy of their slides which are appended to these minutes.

2. GI National Baseline Survey, Innovative Medical Research

Dr Robert Sandler, University of North Carolina, Chapel Hill, NC. Attachment 2

- This large survey involved 2510 households, selected at random from US telephone directories. One person per household was interviewed about any GI symptoms (pain, bloating, loose stools) that they had experienced in the past month.

- The results were as the follows:

- episodic digestive complaints, including pain, bloating and loose stools are common - more than 40% of respondents reported one or more symptom episodes
- 71% perceive their symptoms as moderate to severe in intensity; >50% have some activity limitations; 9 - 19% consult their physician and 43 - 60% take medications
- of those with symptoms, 21 - 24% experienced symptoms in the previous 24 hours
- a number of foods such as beans, onions and spicy foods commonly produce digestive complaints but people eat them anyway

- Dr Sandler concluded that episodic digestive complaints are common and it is therefore not surprising that high levels of such complaints are reported during the olestra post-marketing surveillance.

3. Overview of the effects on stool consistency of olestra ingestion in pigs and in adults.

(Dr John McRory, Procter & Gamble, Cincinnati, OH). Attachment 3

- The presentation provided an overview of models to explore the relationship between digesta viscosity, colonic motility and GI symptoms.

- The conclusions were as follows:

[NZ: Please check – you wanted to amend these, taken from Dr. McRorie's presentation]

- controlled studies in which there is ad lib consumption of snacks made with olestra demonstrate no increase in GI symptoms reporting compared with placebo.
- the increase in reports of GI symptoms with daily consumption of olestra at amounts of 20g/day or greater, may be explained by the physiological response to an increase in fecal bulk and fecal softening.
- unlike sorbitol which is osmotically active and demonstrates a rapid, predictable response, the GI effects of olestra exhibit a gradual dose-responsive onset (days) similar to dietary fiber.
- the results support that GI effects, when they occur in those consuming olestra do not pose a health risk, are not unique to olestra and are in all likelihood due to decreasing stool rheology.

4. Home consumption study of olestra or triglyceride potato chips and corn chips among adults and children

(Dr Robert Sandler, University of North Carolina, Chapel Hill, NC)

- This RCT of potato chips was conducted in approximately 3225 individuals (including >600 children and >400 seniors) over 10 weeks in two locations (St Petersburg, FL and Phoenix, AZ). It assessed the incidence, severity and implications on daily living of common GI complaints in adults and children consuming olestra containing snacks under market conditions.
- The participants kept a daily record of chip consumption, GI symptoms (from a check list), impact on daily life and physician contact.
- The results will be ready in February 1998 but the preliminary data indicates that the drop out rate is low and only one person withdrew due to GI symptoms. The average chip withdrawal for the Olean and the TG chips was similar at 3 bags/week/household.

5. Update on test market statistics

(Dr. Nora Zorich, Procter & Gamble, Cincinnati, OH). Attachment 4

- There have been no major changes in test market status in Columbus (Pringles) and Indiana (Pringles and Frito Lay) since the June meeting.
- The total monthly call volume was high in April (262 people reporting symptoms). This corresponded with the Indiana launch. Thereafter the monthly call rate from May to October inclusive varied from 68 to 11 calls per month. There were 446 reports in total in the period 22nd March to 22nd July 1997. See Attachment 5.
- The physician contacts during this period were:

	April - July	August - October
Office visit	18	2
ER visit	12	5
Hospital visit	1	0

6. Update on the rechallenge test data

(Dr. Nora Zorich, Procter & Gamble, Cincinnati, OH). Attachment 6.

- 100 consumers have been enrolled in the rechallenge study. The data are consistent with previous results from earlier cohorts completing the study and continue to support the conclusion that the majority of the reports received cannot be causally associated with olestra consumption.

7. Global review of all spontaneous adverse reports

(a) Does the dose of olestra consumed affect the type and severity of the alleged adverse events? *(Dr Dennis Ahnen, VA Hospital, Denver, CO). Attachment 7*

- With consumption of up to 30 grams of olestra there was no effect of dose on the incidence or the type of adverse events reported. Above this the number of reports was too small to draw meaningful conclusions.
- There was no effect of dose on the severity of abdominal pain, diarrhea or nausea and vomiting. However, in doses >30-40 grams of olestra there was an increase in the incidence of flatulence but the numbers of individuals is very small.

(b) Does the dose of olestra consumed affect the symptoms onset and duration?

(Dr. James Freston, University of Connecticut, Farmington, CT). See Attachment 8.

- Most symptoms such as nausea, diarrhea and abdominal pain occur within 15 - 20 hours and are independent of dose . It was concluded that these early onset symptoms cannot be attributed to olestra and may be due to high background incidence of this type of symptom and the effects of other food consumption.

(c) Does the age of the consumer influence the alleged reports?

(Dr. Steven Czinn, Rainbow Babies & Children's Hospital, Cleveland, OH). See Attachment 9.

- Comparing the very young and the very old, there were no meaningful differences in the incidence and type of adverse report. There are rather more severe symptoms in the >65 age group but this might be a consequence of the relatively small sample size.

8. Review of the algorithm agreed at the last meeting for evaluating reports of suspected events associated with olestra

(Dr. Judith Jones, The Degge Group Ltd., Arlington, VA)

- It was agreed that the algorithm was satisfactory and did not require further modifications. It was used to review the 'serious' adverse events described below.

9. Review of 'serious' adverse events (i.e. death or life threatening, requiring hospitalization, a visit to an emergency room or a physician visit.

- There were a total of reports which fell in the serious category and 8 which required physician contact. The narrative for each case was read out by a member of the Committee to ensure that everyone was aware of all the case details. The algorithm was then systematically applied and the association of the event with olestra consumption was then voted upon by the Committee. Attachment 10.
- There were only 4 cases where any association with olestra could be considered, for the others the relationship was considered unlikely. Even when an association was sited as 'possible' this was usually because a causal relationship could not be *excluded* and was therefore assigned a 'possible' association by default. The Committee also discussed the seriousness of each case and the verdict is sited below:

patient number 965: the rash was not considered serious and resolved on its own but was "possibly" related to olestra consumption.

(Inter alia discussing this case, the Committee thought it might be helpful at the next meeting to focus on allergic symptoms and it was decided that Dr Zorich would identify a suitable guest expert to join the Committee at the next meeting).

Patient number 182: the GI symptoms reported by this 70 year old man were not considered serious and the Committee considered there was a weak possibility that they were related to olestra consumption

Patient number 184: the Committee's views were split on the report of this 11 year old boy whose mother reported that he had 7 watery bowel motions which necessitated an ER visit. Three of the Committee members thought that any association was unlikely and one felt that it was possible, but all the members agreed that the event was not serious.

Patient number 245: it was felt that the diarrhea and pain experienced by this woman who ate Pringles which contained olestra could possibly have been due to the olestra but this was not serious.

- In all other cases (n=.....) there was not considered to be any association between the reported events and the consumption of olestra.

10. Conclusions

- The Committee concluded that :

The type, severity and duration of symptoms reported in the olestra passive surveillance program does not pose any cause for medical concern.

Code: PMSMINUTES – Version 1
Date: December 16th 1997 (JOD)

Olestra Post Marketing Surveillance Committee

4th Meeting
February 10th, 1998



STRATEGIC · CONSULTANTS · INTERNATIONAL · plc

17 March, 1998

AH/JOD/PMSC/FDAMSL.DOC

Dr. M. D. Ditto, PhD
Food and Drug Administration
Office of Premarket Approval HFS-206
200 C Street
South West
Washington D.C.
20204
USA

Dear Dr. Ditto,

Re: Minutes of Olestra Post Marketing Surveillance Committee

Please find enclosed copies of the Minutes based on the findings of a recent meeting of the Olestra Post Marketing Surveillance Committee which was convened on February 11th, 1998 to review the adverse events reported by people consuming olestra-containing foods in the period October 22nd, 1997 through January 9th, 1998. The objective was to determine if these reports indicated any cause for medical concern. The panel is comprised of experts in the fields of gastroenterology, pharmacovigilance and epidemiology. The meeting was convened independently by Strategic Consultants International UK, and was funded by Procter & Gamble.

For convenience, Procter and Gamble asked SCI to submit these Minutes to you directly and we understand that they have already discussed this with you.

Questions about the Minutes per se and the experts' roles should be directed to SCI, but any points concerning the data should be directed to Procter and Gamble.

Yours sincerely,

PP
Alison L. Howe

ALISON L. HOWE
Managing Director
Strategic Consultants International
Direct Line 44-(0)1442-210161 (UK)

Encs: Minutes

Minutes of the Olestra Post Marketing Surveillance Committee (4th Meeting)

Chicago, February 10th, 1998

Attendees: R. Sandler : Chairman, University of North Carolina, Chapel Hill, NC
D. Ahnen : VA Hospital, Denver, CO
S. Czinn : Rainbow Babies and Childrens Hospital, Cleveland, OH
J. Freston : University of Connecticut, Farmington, CT
J. Jones : Degge Group Ltd, Arlington, AV
N. Zorich : *Presentation only, Procter & Gamble, Cincinnati, OH*

1. Update on the test market statistics

- In the period April 1996 through February 1998 the test markets for olestra-containing snacks have involved the following manufacturers and test cities:
 - *Frito-Lay*: Eau Claire, WI; Cedar Rapids, IA; Grand Junction, CO – completed
: Greater Indianapolis, IN - initiated February 24th 1998 and is ongoing
 - *Pringles*: Columbus, OH – initiated September 20th 1997 and is ongoing
: Central Indiana - initiated March 24th and is ongoing
 - *Nabisco*: Marion, IN – initiated April 21st 1997 and is ongoing
- In the period from April 1996 there have been 5 million servings of olestra – containing snacks in the Pringles family of products (3.3 million in Ohio and 1.7 million in Indiana) and 17 million servings of the Frito-Lay family of products in Indiana.
- With respect to the calls to Procter & Gamble concerning their Pringles range of products the categories of calls are as follows:

Testimonials	1359 (26%)
Information	3004 (57%)
General complaints	508 (9.6%)
Symptom complaints	439 (8.3%)

2. Expansion of the Olestra Post Marketing Surveillance Program to accommodate the national expansion

2.1 *Refinements to the data collection processes*

- Over the next few months Olestra containing snacks will become available nationally. This will be associated with an increase in the number of consumer reports (see below for the anticipated volume of calls). Procter & Gamble have put

in place a plan of action and extended resources to meet the responsibilities for monitoring the marketed product.

- Extrapolating from the test market experiences, 143,000 calls reporting adverse events are anticipated over the first 12 months. The volume will be highest in the first 2-3 months and then plateau. About 10% of these calls will involve the consumer seeing a physician (approx 1400 calls).
- In order to optimize the reporting processes, and to maintain the quality of the surveillance programs, the individual snack manufacturers will collect the data for reports which do not involve a physician visit. This data will then be transferred electronically to Procter & Gamble to manage (see appendix 1 for a flow plan of this process). Calls involving a physician visit (approximately 10%) will be transferred directly to Procter & Gamble who will focus on collecting substantive medical information concerning the report.

2.2 Data to be reviewed by the Olestra Post Marketing Surveillance Committee

- With the national expansion, the *Post Marketing Surveillance Committee* decided that in the future it will focus its attention on those consumer reports involving a physician visit. They requested that the information be presented as follows:
 - For those reports *which involve physician contact*: tabulated reports of the duration of the symptoms and the amount of olestra consumed.
 - For reports *involving hospitalization or a visit to an Emergency Room*, the Committee asked to be supplied with narratives. These narratives will be divided among the Committee members who will review the reports and apply the safety surveillance algorithm the Committee have developed. Those reports which pose a cause for concern will be brought forward for discussion at the Committee meeting.
- Procter & Gamble are initiating a Medical Communications Program which will provide medical information to physicians and other health care professionals regarding olestra consumption in their patients (e.g. effects on the GI tract, vitamins, carotenoids, medications etc).
- This information will equip physicians to answer patients' questions, to address their own questions/ concerns and to help them appropriately assess the implications of olestra consumption in their individual patients.
- The information will be provided by a professionally manned 1-800 Helpline, through a Professional Education Mailer and an Olean Web Site will provide information specifically for health care professionals.

3. Review of all spontaneous adverse event reports during the period October 22nd through January 9th 1998 (not involving a physician visit)

3.1 Individual reports

- Dr Czinn, Dr Freston and Dr Jones reviewed the reports numbered 1301292 – 1301325 and drew the Committee's attention to the following reports which were discussed and evaluated for their possible association with olestra consumption.

ID 1301309

The consumer was a 10 year old girl who developed 5 days of diarrhea, abdominal cramps and headache 10 minutes after consuming 6 chips (Pringles) containing olestra (approx 3 grams).

The Committee did not consider the report to be associated with olestra consumption

ID 1301317 and 1301318

These two consecutive reports involved a husband and wife who reported cramping and diarrhea 12 hours after consuming 17 grams of olestra . The cramping lasted 8 days and the diarrhea 2 days.

The Committee did not consider that the reports were related to the consumption of olestra.

ID 1301327

The consumer reported developing gas and diarrhea within 2 hours of eating of wheat thins on four separate eating occasions. On three of the four occasions the consumer developed hives . The condition resolved within 2 hours of taking Benadryl.

The Committee considered that the report was probably related to the consumption of wheat thins (but not to olestra per se) but the adverse event was not serious.

ID 1301389, 1301390, 1301391

A 43 year old woman reported a rash which lasted 1-2 days after consuming 8.1 grams olestra

The Committee considered that this these three cases had been reported on one call and that the adverse events were unlikely to be related to the consumption of olestra.

3.2 Does the dose of olestra consumed affect the type and severity of alleged adverse events?

- Dr Ahnen reported that there was no dose-related pattern to the adverse events reported.
- Dr Freston reported that there was no relationship between the dose of olestra consumed and the symptom onset and duration
- Dr Czinn reported that the age of the consumer did not influence the alleged reports.

4. Review of individual case reports involving physician contact

- The Committee reviewed the following consumer reports which involved a physician contact. The algorithm developed by the Committee to evaluate the possible relationship of the event to the olestra consumption was applied in each case.

ID 1301306

A 58 year old woman who had reported abdominal pain and diarrhea (maximum of 2 watery bowel movements per hour) within 3 hours of consuming a 'handful' of olestra-containing Ruffles. The consumer presented to the emergency room who discharged her with instructions to take clear fluids for 24 hours and Maalox if required.

The consumer had a history of fibromyalgia and at the time of the report took antidepressants/antianxiolytics, a diuretic and antiarthritics.

The Committee considered that it was unlikely that the symptoms were related to the consumption of olestra

ID 1301320

A 63 year old woman who had eaten 2 ounces of olestra-containing chips on August 4th 1997 and complained of diarrhea and cramping within 12 hours of their consumption. She presented to the emergency room on September 10th 1997 and was given fluids intravenously.

The Committee considered the association was unlikely as over a month had elapsed between the ingestion of the olestra-containing chips and the visit to the ER.

ID 1301324

A 30 year old man consumed 5 Nacho chips on August 10th. He reported cramping and gas on 12th August which persisted until he went to the emergency room on August 13th. He was treated with an enema.

The Committee thought that the association of the symptoms and the consumption of olestra was unlikely and there was some other explanation for them. It was noted that an enema was an inappropriate treatment for the complaint.

ID 1301328

The father of a 7 year old reported that his daughter consumed one half of an unspecified amount of olestra-containing chips. Within 30 minutes she experienced stomach cramping and within one hour vomiting. She also complained of headache and felt weak. She was taken to the emergency room and was treated with a suppository and unspecified iv medication for the pain. The child was subsequently taken to a pediatrician who thought that the child had 'food poisoning, but that many children in the area had the flu'. The father heard a report about olestra on NBC and returned to the shop where he purchased the chips to check the ingredients. The manager said that olestra products were not being sold and had never been available.

The Committee considered that the symptoms were unlikely to be related on two accounts: olestra was not available at that time in California and the child had 'flu.

ID 1301341

A 45 year old woman who was awakened at 2am after consuming 2 ounces of olestra-containing chips the evening before. She went to hospital within 24 hours of the onset of the symptoms. She had an ultrasound and states that the physician reported that she had diverticulitis. The consumer thought that the incident was not connected to olestra consumption as she had been eating the product for almost one year with no problems.

The Committee considered that it was unlikely that the symptoms were related to the consumption of the olestra-containing chips as she had no recurrence of symptoms on reingestion.

ID 1301356

A 76 year old woman reported that she experienced abdominal and back pain as well as loss of appetite and strength within 12 hours after eating 2 ounces of an olestra salted snack. The abdominal and back pain resolved after 3 weeks, the loss of appetite after six weeks and the loss of strength after 3 months.

The Committee felt that the symptoms were unlikely to be related to the consumption of the olestra-containing chips as they did not disappear after the discontinuation of the product.

5. The Committee's conclusions

- Since this was the last Committee meeting before olestra becomes available nationally, a statement was developed which summarized the Committee's conclusions based on a careful review of the 1376 adverse events reported during the first 22 months of the olestra test marketing program:

- There was no increase in the incidence of morbidity.
- Reports were consistent with the background prevalence of mild, self limiting digestive symptoms commonly occurring in the population (eg IBS, viral illnesses etc).
- No consistent dose response was identified for these common GI symptoms (diarrhea and cramping). However, there were a few cases of oily stool following very high doses of olestra.
- There is no reason to believe that, based on this information, olestra represents a cause for public health concern.

6. The date for the next Committee meeting was set as 1st May 1997

Olestra Post Marketing Surveillance Committee

5th Meeting
April 30th / May 1st, 1998

5th Olestra Post Marketing Surveillance Committee

Boston - April 30th/May 1st 1998

AGENDA

April 30th: Part 1

Re-assessment of 1-800 reports which involved physician contact using final algorithm reviewed at first two committee meetings

All

May 1st: Part 2

**National roll-out and call volume.
Aggregate data from 1-800 telephone number**

***R. Midday
K. Roll***

These data will be presented in tabulated form and discussed by the overall group

Review of 1-800 reports involving physician contact during the national launch period

***Led by
R. Sandler***



STRATEGIC · CONSULTANTS · INTERNATIONAL · plc

10th June, 1998

AH/CPC/PMSC/FDAMSL.DOC

Dr. M. D. Ditto, PhD
Food and Drug Administration
Office of Premarket Approval HFS-206
200 C Street
South West
Washington D.C.
20204
USA

Dear Dr. Ditto,

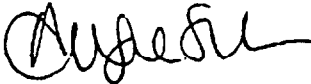
Re: Minutes of the 5th Olestra Post Marketing Surveillance Committee

Please find enclosed copies of the Minutes based on the findings of a recent meeting of the Olestra Post Marketing Surveillance Committee which was convened on May 1st, 1998 to review the adverse events reported by people consuming olestra-containing foods in the period January 23rd, 1998 through April 22nd, 1998. The objective was to determine if these reports indicated any cause for medical concern. The panel is comprised of experts in the fields of gastroenterology, pharmacovigilance and epidemiology. The meeting was convened independently by Strategic Consultants International UK, and was funded by Procter & Gamble.

For convenience, Procter and Gamble asked SCI to submit these Minutes to you directly and we understand that they have already discussed this with you.

Questions about the Minutes per se and the experts' roles should be directed to SCI, but any points concerning the data should be directed to Procter and Gamble.

Yours sincerely,

PP 

ALISON L. HOWE
Managing Director
Strategic Consultants International
Direct Line 44-(0)1442-210161 (UK)

Encs: Minutes

Minutes of the Olestra Post Marketing Surveillance Committee (5th Meeting)

Boston, April 30th/May 1st 1998

Attendees:	R. Sandler	: Chairman, University of North Carolina, Chapel Hill, NC
	D. Ahnen	: VA Hospital, Denver, CO
	S. Czinn	: Rainbow Babies and Childrens Hospital, Cleveland, OH
	J. Freston	: University of Connecticut, Farmington, CT
	J. Jones	: Degge Group Ltd, Arlington, AV
	N. Zorich	: <i>Presentation only, Procter & Gamble, Cincinnati, OH</i>
	B Middy	: <i>Presentation only, Procter & Gamble, Cincinnati, OH</i>
	K Roll	: <i>Presentation only, Procter & Gamble, Cincinnati, OH</i>

1. **Reassessment of the 1-800 reports which involved physician contact, using the final algorithm reviewed at first two committee meetings.**

Since the format of the algorithm used to evaluate the adverse event reports was not finalized until the third Committee meeting, it was decided to reassess the case reports involving physician contact submitted to the first and second Committee meetings using the final algorithm.

Their assessment of these cases is as follows:-

Report #	Association with olestra
1300011	Unlikely
1300060	Unlikely
1300166	Unlikely
1300213	Unlikely
1300223	Unlikely
1300225	Unlikely
1300258}	Insufficient info to apply algorithm
1300259}	
1300336	Unlikely
1300337	Insufficient info to apply algorithm
1300347	Unlikely
1300391	Unlikely
1300394	Unlikely
1300430	Unlikely
1300470	Arrhythmia: unlikely – Oil-in-toilet possible
1300487	Unlikely
1300521	Unlikely
1300616	Unlikely
1300625	Insufficient info to apply algorithm
1300631	Unlikely
1300650	Unlikely
1300655	Insufficient info to apply algorithm
1300778	Insufficient info to apply algorithm
1300789	Unlikely

2.1. National roll out and call volume.

- The total population covered to date by the launch is at least 40 million. From this there were 4061 calls, with 128 physician visits. This is 5-10 fold lower than would have been projected from test market experience.
- Calls from consumers reporting symptoms are less than 3% of the total call volume.
- The calls coming into Frito-Lay involving a physician contact are transferred to Procter & Gamble for follow up.
- The data collected on calls with no physician contact includes:-
 - Date of report
 - Reporter's initials and relationship to the person experiencing the event (if not the same person)
 - Details of the person experiencing the event:-
 - Initials
 - Age, gender
 - City, state
 - Brand of potato chip consumed
 - Amount of olestra consumed
 - Symptoms
 - Overall severity (consumers asked to quantify effect of symptoms on activity level)
- For calls involving a physician contact the following, additional data is collected:-
 - Type of visit
 - Medical history
 - Duration of olestra consumption (# eating days)
 - Time of onset and resolution
 - Narrative about event
 - Medical follow up (if possible)

2.2. Assessment of aggregate data from 1-800 telephone numbers.

- The Committee reviewed the aggregate data from the 1-800 telephone numbers. This was presented as a series of tables.

Exhibit 1: Test market and national – physician contacts.

The percentage of total individuals reporting physician contact decreased from 6.5% during the test markets to 3.2% during the national launch.

Exhibit 2: Most frequently reported symptoms.

The symptoms reported in national and test market were similar, with the majority being gastrointestinal in nature. GI symptoms were also the most frequently reported symptoms by the subset of consumers reporting physician contact. While the overall proportion of consumers reporting rash and urticaria were similar in national (rash 1.7% - urticaria 1.4%) and test market (rash 1.3% - urticaria 0.7%), a difference was noted in the physician contact subset where a higher proportion of consumers in national (rash 14.2% - urticaria 11.7%) versus test market (rash 4.7% - urticaria 5.8%) reported these symptoms. This was particularly due to the lower percent of callers reporting physician contact in national (3.2%) compared to test market (6.5%). The committee agreed that olestra itself should not be allergenic. The committee noted that skin rash was a common report during the introduction of the food additive aspartame and recommended that P&G have an allergy expert review these reports.

Exhibit 3: Age and sex of consumers reporting symptoms.

No difference in symptom reporting by age groups.

Exhibit 4: Amount of chips containing olestra consumed by those reporting symptoms.

The vast majority of consumers who reported symptoms when consuming olestra containing chips had eaten 2.0 oz. or less

Exhibit 5: Distribution of amount of olestra consumed.

The most frequently consumed amount of potato chips in those reporting symptoms was between 1-2 oz.

Exhibit 6: Duration of olestra consumption.

The vast majority of consumers had eaten olestra containing products on 1 day only at the time of reporting the adverse event.

Exhibits 7/8/9: Alleged adverse PER reported by reported term.

The Committee reviewed the frequency of symptom reports and concluded that there was no cause for medical concern.

Exhibit 10: Numbers of consumers reporting each event.

See exhibit 2 for comment.

Exhibits 11-16: Symptoms by amount of olestra consumed.

The Committee concluded that there was no dose response, but the number of reports was very small at the higher doses.

Exhibit 17: Maximum duration of symptoms.

For reports not involving physician contacts, the majority of events last for a day or less. For events associated with a physician contact, a third of the events lasted for 3 or more days.

Exhibit 18: Symptoms and age.

Overall the adult consumers reported more abdominal pain, diarrhea and flatulence than the <5 year olds. The younger consumers had more vomiting than other age groups. For those with physician contact, the adult consumers reported more abdominal pain and flatulence, but the incidence of diarrhea, vomiting and nausea were similar in all groups (slightly higher nausea in the >65 years). The incidence of rash, fever, headache and pruritis was higher in the 6-11 age group, but the number of reports is very small (3 or less per category).

Exhibit 19: Overall symptoms severity.

There is an apparent change in the symptom severity between the test and national data. This was because the method of logging severity changed (during the national launch severity of symptoms were qualified according to impact on activity index). The severity of symptoms did not change for symptoms associated with physician contact.

Exhibit 20: Symptom severity by dose.

There was no dose response in the amount of olestra consumed and the severity of symptoms.

Exhibits 21 & 22: Symptom severity by age.

There was no apparent change in symptom severity by age group.

Exhibit 23: Time of onset of symptoms by dose.

There was no relationship between the amount of olestra consumed and the time to onset of diarrhea or abdominal cramping.

3. Review of 1-800 reports involving physician contact during the national launch period.

The reports involving physician contact were divided up among individual members of the Committee, who assessed each report within their allocation. For straightforward cases there was agreement that an association with olestra was unlikely. The following reports were discussed in greater detail and assessed to be possibly or probably related to olestra. In some cases there was insufficient data to make this assessment.

Report #	Association with olestra
130412	Possible, not serious
130429	Unlikely
130442	Unlikely
130443	Unlikely
130454	GI symptoms: 3 members: unlikely; 1 member: possible Rash: unlikely
130456	Unlikely
130476	Unlikely
130486	Unlikely
1301950	Unlikely
1301952	Unlikely

Report #	Association with olestra
1302535	Unlikely
1302769	Possible, non serious
1302771	Unlikely
1302773	Insufficient information
1302774	Unlikely
1302870	Unlikely
1302872	Unlikely
1302875	Insufficient information
1302957	Unlikely
1302963	Unlikely
1303128	Unlikely
1303132	Unlikely
1303255	Insufficient information
1303258	Unlikely
1303389	Unlikely
1303392	Unlikely
1303536	Unlikely
1303766	Unlikely
1303769	Unlikely
1303795	Insufficient information
1303796	Unlikely
1303990	Unlikely
1304118	Unlikely
1304122	Unlikely
1304125	Unlikely
1304219	Unlikely
1304222	Unlikely

1304359	Unlikely
1304363	Unlikely
1304751	Insufficient information
1304753	Unlikely
1304758	Unlikely
1304758	Unlikely
1304759	3 x unlikely 1 x insufficient information
1304844	Unlikely
1304845	Insufficient information
1304846	Possible, non serious
1304847	Unlikely
1304931	Unlikely
1304932	Unlikely
1304981	Unlikely
1304985	Unlikely
13049986	Insufficient information
1304987	Unlikely
1304988	Unlikely
1304998	Unlikely

The Committee concluded that there is no reason to believe that, based on this information, olestra represents a cause for public health concern.

Olestra Post Marketing Surveillance Committee

6th Meeting
October 15th, 1998

**Olestra Post Marketing Surveillance Committee
(6th Meeting)**

AGENDA

**The Westin Hotel, Copley Place, Boston, MA
October 15th, 1998**

7:30-8:30am	<i>Buffet breakfast</i>	
8:30-8:45am	National launch statistics and discussion of selected issues: <ul style="list-style-type: none">• Allergy reports• Vitamin K	<i>K. Roll</i>
8:45-9:15am	Review of Committee's objectives post launch	<i>R. Sandler</i>
9:15-10:00am	How to assess safety: the evolving role of the algorithmn?	<i>R. Sandler J. Jones</i>
10:00-10:20am	<i>Coffee</i>	
10:20-11:30am	Review of physician contact narratives, focusing on cases of note	<i>All</i>
11:30-12:30am	Review of aggregate tables <ul style="list-style-type: none">• Does the dose of olestra consumed affect the type and severity of the alleged adverse events?• Does the dose of olestra consumed effect symptom onset and duration?• Does the age of the consumer influence the alleged reports	<i>R. Sandler J. Freston S. Czinn</i>
12:30-12:40pm	Conclusions: does the type, frequency, severity and duration of symptoms reported in the olestra passive surveillance program pose any cause for concern?	<i>led by R. Sandler</i>
12:45pm	<i>Lunch</i>	



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February 23rd 1999

AH/JOD/6th PMSC/FDAMSL.DOC

Mary Ditto PhD
Food & Drug Administration
1110 Vermont Avenue, NW
HFS-207, 12th Floor
Washington, DC 20005
USA

Dear Dr. Ditto,

Re: Minutes of olestra Post Marketing Surveillance Committee

Please find enclosed copies of the Minutes based on the findings of a recent meeting of the 6th Olestra Post Marketing Surveillance Committee which was convened on October 15th 1998 to review the adverse events reported in the program by people consuming olestra-containing foods. The objective was to determine if these reports indicated any cause for medical concern. The panel is comprised of experts in the fields of gastroenterology, pharmacovigilance and epidemiology. The meeting was convened independently by Strategic Consultants International UK, and was funded by Procter & Gamble.

For convenience, Procter and Gamble asked SCI to submit these Minutes to you directly and we understand that they have already discussed this with you.

Questions about the Minutes per se and the experts' roles should be directed to SCI, but any points concerning the data should be directed to Procter and Gamble.

Yours sincerely,

ALISON L. HOWE
Managing Director
Strategic Consultants International
Direct Line 44-(0)1442-210161 (UK)

Encs: Minutes

**6th Olestra Post Marketing
Surveillance Committee**

**The Westin Hotel, Boston, MA
October 15th, 1998**

**Prepared by:
Strategic Consultants International
Quantum House
Maylands Avenue
Hemel Hempstead
Herts HP2 4SJ UK
Tel: 011-44-1442-210161
Fax: 011-44-1442-210169
Date: February 4th 1999
Code: 6TH PMSC\MINUTES (JOD)**

6th Olestra Post Marketing Surveillance Committee

The Westin Hotel, Boston, MA

October 15th, 1998

Attendees: **R. Sandler** : Chairman, University of North Carolina, Chapel Hill, NC
 S. Czinn : Rainbow Babies and Childrens Hospital, Cleveland, OH
 J. Freston : University of Connecticut, Farmington, CT
 J. Jones : Degge Group Ltd, Arlington, AV
 G. Allgood : *Presentation only, Procter & Gamble, Cincinnati, OH*
 K Roll : *Presentation only, Procter & Gamble, Cincinnati, OH*

Contribution
By e-mail: **D. Ahnen** : VA Hospital, Denver, CO

1. Introduction and objectives of meeting

Dr Robert Sandler summarized the post-FAC objectives of the Olestra Post Marketing Surveillance Committee as follows:

- To review the safety of olestra. In particular to look for signals of possible public health concern
- To recommend follow up activities in these areas (expert opinion; studies etc.)
- To reach consensus on whether or not any health effects constitute a public health issue

2. National launch statistics

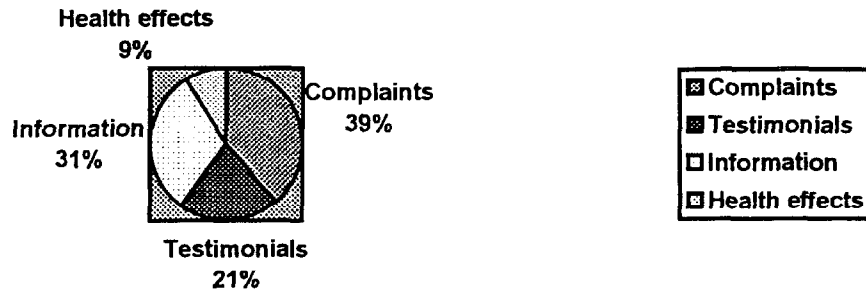
In the period from the national launch of olestra to Labor Day 1998, over 1 billion servings of olestra – containing snacks have been distributed.

The number of callers reporting alleged symptoms following consumption of olestra has dropped from 1 per 20,000 servings during the Test Market to a current level of 1 per 80,000 servings.

Figure 1 illustrates the distribution of the consumer comments :

- Complaints 39%
- Testimonials 21% (unprecedentedly high compared to other Procter & Gamble food products)
- Information 31%
- Health effects 9%

The distribution of the consumer comments:



Reports which include a physician contact are now at approximately 5 per week.

3. Future of Olean from P&G's perspective and future plans

Greg Allgood, Procter & Gamble, gave a brief update of P&G's plans for possible future food categories for Olean and on interactions with the FDA post -FAC.

The Committee expressed dissatisfaction with the FDA's apparent lack of follow up post-FAC on the issue of the interim label. The Committee discussed the current wording of the label and agreed that it is not an accurate reflection of either the clinical studies involving olestra, or of the extensive post marketing surveillance safety database which the Committee had personally reviewed in depth. Moreover, the current label does not acknowledge the conclusions of the FAC which recommended a change to the label.

The Committee agreed with Dr Sandler's recommendation to express their concern in writing to the FDA.

4. Review of the Committee's objectives post launch and the evolving process of assessing safety

The Committee discussed their objectives in the post-FAC/ post-launch period.

These were agreed as follows:

- To review the safety of olestra. The role of the safety algorithm was discussed and it was agreed that while it had played a valuable role in triaging adverse events and providing a consistent structure for the review of adverse events prior to the FAC, it was too constricting for current use. Moreover, it was problematic for application to high incidence background conditions in the general population; such as GI disorders as there was rarely sufficient data to apply the full algorithm.

- It was agreed to modify the review process as follows and this was piloted in this meeting.
 - The aggregated data will be reviewed in tabular form and the Committee will request further information only if any potentially relevant signals are observed
 - Consumer reports which involve contact with a physician will be divided into batches and assigned to individual members of the Committee ahead of the meeting. The Committee members will review the reports for which they are responsible and will flag any which they feel should be reviewed by the full Committee. These individual reports will be reviewed by the group, any possible association with olestra will be discussed. The causality to olestra will be assigned as either "unlikely causality" or "needs further assessment". These later reports will be subclassified to note if there was a rechallenge, or not, by the consumer and/ or health professional. These events will also be evaluated against the FDA criteria for serious ADE.
 - The algorithm for evaluating reports will be used as a guidance tool.

5. Issues with respect to allergy; vitamin K

5.1 Allergy

Allergy reports were noted and discussed by the Committee. When all reports are taken together allergy accounted for less than 1 report per million servings sold or sampled; approx. 3.4% of total adverse event reports during the 9th quarter. In the context of reports involving a physician visit, the percentage of allergy reports accounted for 27.6%. The Committee members were unanimous that in their opinion olestra is not responsible for allergic reactions per se; other components of the diet are more likely to be the cause.

Dr Czinn advised that children be included in any clinical diagnostic investigation since they appear to have a higher rate of occurrence of allergic-type reactions than adults, both in the clinic setting and in the Health Effects reports, as a percentage of allergy-type symptoms by age group (rash, pruritus, urticaria). Dr Czinn did note, however, that the total number of such reports involving children is small. Dr Jones suggested tracking putative allergy reports by product to see whether the distribution clusters to certain products, although to date this has shown no difference.

The Committee recommended the following action points:

- appoint allergy experts to review the allergy issue (in which Dr Jones is involved in order to provide a link between the PMS Committee and the new group.)
- consider rechallenge studies for patients reporting symptoms most characteristic of allergic reactions.

5.2 Vitamin K

Vitamin K is added to Olean snacks to compensate for partitioning into olestra (see figure 2). This is indicated on the labeling in two places. The FDA determined the amount of Vitamin K added (8.0ug/g olestra). Patients taking warfarin who consume olestra snacks are recommended to follow standard guidelines about maintaining a steady diet to minimize fluctuations in Vitamin K intake.

P&G has distributed professional education materials during the national launch and these include information on Vitamin K (see figure 3). P&G is also exploring means of incorporating information into pharmacy databases.

The Committee expressed the opinion that the FDA mandated level appears higher than necessary for compensation and steps should be taken to reduce the amount to avoid impacting coagulation status in patients taking coumadin. The Committee approved of the steps being taken by P&G, but felt that the situation warrants full review and follow up.

6. Review of the aggregate tables

The Committee reviewed the aggregate tables and concluded that:

- the dose of olestra consumed does not affect the severity of the alleged adverse events and does not affect the type of reported adverse event, except abnormal stool, which is to be expected.
- the dose of olestra consumed does not affect symptom onset and duration
- the age of the consumer does not influence the alleged reports

7. Review of physician narratives

The reports involving physician contact were divided among individual members of the Committee, who assessed each report within their allocation. For straightforward cases there was an agreement that an association with olestra was unlikely. Only those reports which had unusual features were discussed by the Committee as a whole. For the following cases there was agreement that an association with olestra was unlikely.

Alert #	Comments
1306143	Unlikely association with olestra
1306638	Unlikely association with olestra
1307165	Unlikely association with olestra
1307550	Unlikely association with olestra
1307749	Unlikely association with olestra

1308466	Unlikely association with olestra
1308542	Unlikely association with olestra
1308621	Unlikely association with olestra
1308706	Unlikely association with olestra
1309248	Unlikely association with olestra
1309808	Unlikely association with olestra
1310292	Unlikely association with olestra
1310336	Unlikely association with olestra
1310476	Insufficient data to assess

For the reports involving allergy (n=46) or coagulation (n=7), the Committee felt that these should be assessed by relevant experts, and requested that P&G identify appropriate allergy experts for this purpose.

The Committee concluded that there is no reason to believe that, based on current information, olestra represents a cause for public health concern.

I do/do not ~~approve the above minutes of the 6th Post Marketing Surveillance Committee for and on behalf of the Olestra Post Marketing Surveillance Committee.~~

Signed:


Dr. Robert Sandler

Date:

1/29/99

*Please complete and return this form to Alison Howe
Strategic Consultants International - Fax: 011-44-1442-210169*

THANK YOU

**7th Olestra Post Marketing
Surveillance Committee**

Teleconference

June 14th, 1999

Prepared by:

Strategic Consultants International
Quantum House
Maylands Avenue
Hemel Hempstead
Herts HP2 4SJ UK
Tel: 011-44-1442-210161
Fax: 011-44-1442-210169
Date: 7 July, 1999
Code: 7th PMSC Minutes (APS)

Launch statistics

More than 1.75 billion servings have been sold or sam

- comments: health effect complaints being 9:1.

Consumer reporting was less than 1 per 350,000 serving

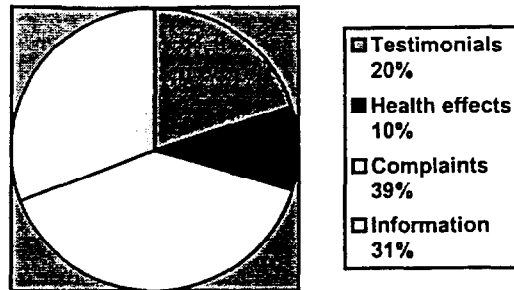
The FDA is reconsidering the label for products containing olestra.

3. Launch statistics Kevin Roll

More than 1.75 billion servings have been sold or sampled since the national launch. The product has been well received with the ratio of product comments: health effect complaints being 9:1.

Consumer reporting was less than 1 per 350,000 servings during the 1st quarter of 1999 – down from 1 per 20,000 during the test markets.

Weekly PMS call volume is down to approximately 40 calls/week, with about two per week reporting a physician contact. The vast majority of reports are GI in nature. The number of reports received each week appears to have levelled off.



The all-symptom reports have dropped from 4951 to 644 per quarter and physician contacts from 200 to 27 since the last PMS Committee.

4. Update on allergy and vitamin K

G. Allgood

The allergy reports have declined from 4.1% during the first reporting period after national introduction to 2.2% in the 12th reporting period. The number of allergy reports with a visit to a physician has declined over the same period from 38 to 7 (NB: Allergy-type reports as a percentage of physician contact has also decreased in this period).

Procter & Gamble consulted with Dr. Steve Taylor, University of Nebraska, Food Processing Center, Dr. Hugh Sampson, Mount Sinai Medical School and Dr A. Wesley Burks, Arkansas Children's Hospital/University of Arkansas concerning the possibility that olestra could cause allergic reactions. They were in agreement that olestra is very unlikely to elicit hypersensitivity reactions. They considered that the symptoms in a small subset of reports are consistent with allergic reactions and cannot be ruled out by history alone. A double-blind, placebo-controlled re-challenge study could be performed to determine whether olestra, or the added vitamin system, is capable of eliciting immediate food hypersensitivity reactions in a small subset of the population.

This study will be performed by Procter & Gamble. The investigator will be Dr. A. Wesley Burks. The study will be conducted at the Arkansas Children's Hospital, Department of Pediatric Allergy and Immunology. The goal will be to recruit 20 subjects reporting symptoms characteristic of IgE-mediated food hypersensitivity (urticaria and rash). Subjects will receive a serving of olestra at least equal to that alleged to have caused symptoms (min 2oz of olestra-containing/TG-containing chips in adults). A standard hypersensitivity symptom reporting tool for DBPCFC (Double-Blind, Placebo-Controlled Food Challenge) will be used.

The PMS Committee requested to see the results of this study.

The members also requested that an allergy expert, Dr. Steve Taylor, join the PMS Committee.

5. Vitamin K

G. Allgood

In the clinical cross-section study of the olestra Post Marketing Surveillance Study there had been no change in vitamins (retinol, 25-OH vitamin D, α -tocopherol) except vitamin K₁. The level of this latter vitamin had increased on medium/high consumption of olestra but this involved small numbers of people.

In the cohort study there was no change in the concentration of fat-soluble vitamins (vitamins A, D and E). There was an increase in vitamin K in those consuming >2g olestra a day. Expert opinion stated that this change might be expected with a serving of broccoli and is not clinically significant.

Procter & Gamble has consulted Dr. David Kuter, Head of Thrombosis and Hemostasis, Massachusetts General Hospital (and 4 other coagulation clinics: University of Kentucky, University of Texas, University of Cincinnati and Veterans Administration Hospital, Tampa) to better understand how patients are managed, how they are instructed about their diet and monitored, as well as the clinicians' level of knowledge regarding olestra and vitamin K.

They concluded that warfarin/olestra reports were not clinically impressive and that the INR fluctuations were not significant, with the exceptions of one patient. Overall, the experts concluded that the addition of vitamin K to olestra snacks is no more concerning than adding a few additional helpings of vegetable to the diet and has no significance for ambulatory warfarin patients.

To date, professional education materials have been mailed to 288,000 health care professionals to inform them that patients taking warfarin who consume olestra snacks should continue to follow recommended guidelines for maintaining a healthy diet. This information has also been included in the Olean web site. Relevant information was also included in adverts in 19 medical journals for a period of 3 months.

6. Review of aggregate tables

The Committee reviewed the aggregate tables and concluded that:

- The dose of olestra consumed does not affect the severity of the alleged adverse events, and does not affect the type of reported adverse event.
- The dose of olestra consumed does not affect symptom onset and duration.
- The age of the consumer does not influence the alleged reports.

7. Review of physician narratives.

The reports involving physician contact were divided among individual members of the Committee, who assessed each report within their allocation. Only those cases, which had unusual features, were discussed by the Committee:

Alert #	Comments serious/non-serious	Causality
1311542	serious	unlikely
1311559	serious	unlikely
1311579*	non-serious	needs further assessment
1311863	serious	unlikely
1311911	non-serious	unlikely
1311919	non-serious	unlikely
1311976**	non-serious	needs expert assessment
1312290*	non-serious	needs expert assessment
1311710	serious	unlikely
1315032	non-serious	unlikely
1312333*	non-serious	needs expert assessment
1312554*	non-serious	needs expert assessment
1310631*	non-serious	needs further evaluation
1311087*	non-serious	needs further evaluation
1311438*	non-serious	needs further evaluation
1311192*	non-serious	needs further evaluation
1310938*	serious	needs further evaluation
1311178*	serious	needs further evaluation
1310904	non-serious	not likely
1310645	non-serious	not likely
1311169	non-serious	not likely
1311190	non-serious	not likely
1311277	non-serious	possible
1311337	non-serious	not likely

* These reports are all reports of potential allergies and were reviewed separately by Dr. Steve Taylor who concluded that olestra is unlikely to elicit hypersensitivity reactions.

** This report was of a change in coagulation status and was reviewed by Dr. David Kuter who concluded that olestra is unlikely to bring about clinically significant alterations in coagulation status.

8 **Conclusions**

Based on careful review of aggregate reports and physician reports, the Committee concluded that there was no reason to believe that olestra represents a cause for public health concern.

9. **Future role of PMS Committee**

Bob Sandler

The Committee agreed it was appropriate for Procter & Gamble to send reports to the FDA biannually rather than quarterly since the small number of reports available in a three-month period makes interpretation of data difficult. The Committee expressed interest in seeing the biannual reports and proposed to have 30-60 minute teleconferences, as appropriate, to discuss the reports, in particular those with physician contact and those in which allergy has been reported.

I do do not approve the above minutes of the 7th Post Marketing Surveillance Committee for and on behalf of the Olestra Post Marketing Surveillance Committee.

Signed:


Dr. Robert Sandler

Date:

Aug 16, 1999